

| | Type | L # | Hits | Search Text | DBs | Time Stamp | Comments | Error Definitions | Errors |
|----|------|-----|-------|---|---------------------------------------|---------------------|----------|----------------------|--------|
| 1 | BRS | L1 | 1 | chi-conotoxin | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2004/05/04 09:42 | | | 0 |
| 2 | BRS | L2 | 1 | neuronal adj amine adj transporter | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2004/05/04 09:45 | | | 0 |
| 3 | BRS | L3 | 1 | neuronal adj noradrenaline adj transporter | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2004/05/04 09:45 | | | 0 |
| 4 | BRS | L4 | 1 | chi-mria or chi-mrib | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2004/05/04 09:45 | | | 0 |
| 5 | BRS | L5 | 85362 | pain | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2004/05/04 09:45 | | | 0 |
| 6 | BRS | L6 | 43063 | pain same (treat\$4 or control\$3) | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2004/05/04 09:46 | | | 0 |
| 7 | BRS | L7 | 0 | 1 same 6 | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2004/05/04 09:46 | | | 0 |
| 8 | BRS | L8 | 456 | lewis adj richard.in. | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2004/05/04 09:46 | | | 0 |
| 9 | BRS | L9 | 2 | alewood adj paul.in. | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2004/05/04 09:46 | | | 0 |
| 10 | BRS | L10 | 0 | sharpe adj iain.in. | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2004/05/04 09:47 | | | 0 |
| 11 | BRS | L11 | 2 | sharpe adj i adj a.in. | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2004/05/04 09:47 | | | 0 |
| 12 | BRS | L12 | 459 | (8 or 9 or 10 or 11) | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2004/05/04 09:47 | | | 0 |
| 13 | BRS | L13 | 1 | 12 and 1 | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2004/05/04 09:47 | | | 0 |

FILE 'MEDLINE' ENTERED AT 09:50:40 ON 04 MAY 2004

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FILE 'AGRICOLA' ENTERED AT 09:50:40 ON 04 MAY 2004

=> s chi-conotoxin
L1 4 CHI-CONOTOXIN

=> duplicate remove l1
DUPLICATE PREFERENCE IS 'CAPLUS, EMBASE'
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n
PROCESSING COMPLETED FOR L1
L2 4 DUPLICATE REMOVE L1 (0 DUPLICATES REMOVED)

=> d l2 1-4 ibib abs

L2 ANSWER 1 OF 4 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
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ACCESSION NUMBER: 2004146990 EMBASE
TITLE: Conotoxins as selective inhibitors of neuronal ion
channels, receptors and transporters.
AUTHOR: Lewis R.J.
CORPORATE SOURCE: R.J. Lewis, Institute for Molecular Biosciences, University
of Queensland, Brisbane, QLD 4072, Australia.
r.lewis@imb.uq.edu.au
SOURCE: IUBMB Life, (2004) 56/2 (89-93).
Refs: 20
ISSN: 1521-6543 CODEN: IULIF8
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Cone snails have evolved a vast array of peptide toxins for prey capture
and defence. These peptides are directed against a wide variety of
pharmacological targets, making them an invaluable source of ligands for
studying the properties of these targets in normal and diseased states. A
number of these peptides have shown efficacy in vivo, including inhibitors
of calcium channels, the norepinephrine transporter, nicotinic
acetylcholine receptors, NMDA receptors and neurotensin receptors, with
several having undergone pre-clinical or clinical development for the
treatment of pain.

L2 ANSWER 2 OF 4 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 2003403019 EMBASE
TITLE: Venoms to Drugs 2002 Conference: 14-19 July 2002, Heron
Island, Queensland, Australia.
AUTHOR: Craik D.
CORPORATE SOURCE: D. Craik, Institute for Molecular Bioscience, University of
Queensland, Kalthera Pty. Ltd., Brisbane, QLD, Australia.
d.craik@imb.uq.edu.au
SOURCE: IDrugs, (2002) 5/9 (881-884).
ISSN: 1369-7056 CODEN: IDRUFN
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB As the title suggests, the Venoms to Drugs conference was a highly focused meeting which reported on various aspects of venoms, with particular reference to the development of therapeutic agents from peptidic venom components. While the location on a coral island on the Great Barrier Reef reflected a focus on venoms from marine creatures, venoms from terrestrial animals and toxins from plants were also highlighted in a number of the presentations. Peptide components from the Conus marine snail species featured heavily in the program. Several talks referred to the progression through clinical trials of at least four known conopeptides. Regarding novel disclosures, Bruce Livett from the University of Melbourne gave a particularly interesting report on a newly discovered .alpha.-conotoxin with potential analgesic applications. This molecule is quite distinct from other conotoxins currently in clinical trials for the treatment of pain, and in particular from the .omega.-conotoxin class. .COPYRGT. PharmaPress Ltd.

L2 ANSWER 3 OF 4 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
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ACCESSION NUMBER: 2001134193 EMBASE
TITLE: Composition and therapeutic utility of conotoxins from genus Conus. Patent status 1996 - 2000.
AUTHOR: Jones R.M.; Cartier G.E.; McIntosh J.M.; Bulaj G.; Farrar V.E.; Olivera B.M.
CORPORATE SOURCE: R.M. Jones, Cognetix Inc., 421 Wakara Way, Salt Lake City, UT 84108, United States. rjones@cognetix.com
SOURCE: Expert Opinion on Therapeutic Patents, (2001) 11/4 (603-623).
Refs: 51
ISSN: 1354-3776 CODEN: EOTPEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
032 Psychiatry
037 Drug Literature Index
039 Pharmacy

LANGUAGE: English
SUMMARY LANGUAGE: English
AB With an exponentially increasing body of scientific evidence pointing toward the potential of conotoxins for treatment of a wide variety of nervous system and associated neurological disorders, there has been an explosion of activity in this patent area with more than eighty new patents and PCT publications in the past five years. With the emergence of ziconotide (SNX-111, .omega.-conotoxin MVIIA) as the first clinically used conotoxin for treatment of a neurological disorder, the first part of the new millennium is likely to see many more new filings in this field. The majority of the applications from this period focus on those classes of conopeptides that interact with nicotinic acetylcholine receptors (nAChRs) together with those that block voltage-gated ion channels. This arena has to date been dominated by three research groups: Neurex (a wholly-owned subsidiary of Elan, South San Francisco, CA, USA), Xenome and the Institute for Molecular Bioscience (IMB), University of Queensland (Melbourne, Australia) and Cognetix (Salt Lake City, UT, USA) together with the University of Utah Research Foundation and the Salk Institute for Biological Studies (La Jolla, CA, USA).

L2 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:241270 CAPLUS
DOCUMENT NUMBER: 132:288779
TITLE: Recombinant . ***chi*** .- ***conotoxin***
peptides for inhibiting neuronal amine transporters
INVENTOR(S): Lewis, Richard James; Alewood, Paul Francis; Sharpe, Iain Andrew
PATENT ASSIGNEE(S): The University of Queensland, Australia
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|-------|-----------------|-------|
| ----- | ---- | ----- | ----- | ----- |

WO 2000020444 A1 20000413 WO 1999-AU844 19991001
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,
CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD,
MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
CA 2344765 AA 20000413 CA 1999-2344765 19991001
AU 9964530 A1 20000426 AU 1999-64530 19991001
AU 757011 B2 20030130
EP 1117682 A1 20010725 EP 1999-952156 19991001
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO
JP 2002526098 T2 20020820 JP 2000-574555 19991001
NZ 510813 A 20030829 NZ 1999-510813 19991001

PRIORITY APPLN. INFO.:

AU 1998-6274 A 19981002
WO 1999-AU844 W 19991001

AB The invention relates to an isolated, synthetic or recombinant <<
chi - ***conotoxin*** peptide having the ability to inhibit a
neuronal amine transporter, nucleic acid mols. encoding all or part of
such peptides, antibodies to such peptides and uses and methods of
treatment involving them.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s neuronal (w) (amine or noradrenaline) (w) transporter
L3 43 NEURONAL (W) (AMINE OR NORADRENALINE) (W) TRANSPORTER

=> d his

(FILE 'HOME' ENTERED AT 09:50:17 ON 04 MAY 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
09:50:40 ON 04 MAY 2004

L1 4 S CHI-CONOTOXIN
L2 4 DUPLICATE REMOVE L1 (0 DUPLICATES REMOVED)
L3 43 S NEURONAL (W) (AMINE OR NORADRENALINE) (W) TRANSPORTER

=> s 12 (p) 13
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L16 (P) L9'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L20 (P) L11'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L24 (P) L13'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L26 (P) L14'
L4 1 L2 (P) L3

=> s chi-mria or chi-mrib
L5 9 CHI-MRIA OR CHI-MRIB

=> duplicate remove 15
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n
PROCESSING COMPLETED FOR L5
L6 2 DUPLICATE REMOVE L5 (7 DUPLICATES REMOVED)

=> s 16 not 12
L7 2 L6 NOT L2

=> d 17 1-2 ibib abs

L7 ANSWER 1 OF 2 MEDLINE on STN
ACCESSION NUMBER: 2003482216 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12885787
TITLE: Inhibition of the norepinephrine transporter by the venom
peptide ***chi*** - ***MrIA*** . Site of action, Na+
dependence, and structure-activity relationship.
AUTHOR: Sharpe Iain A; Palant Elka; Schroeder Christina I; Kaye
David M; Adams David J; Alewood Paul F; Lewis Richard J
CORPORATE SOURCE: Institute for Molecular Bioscience and School of Biomedical
Sciences, The University of Queensland, St. Lucia 4072,

Queensland, Australia.
 SOURCE: Journal of biological chemistry, (2003 Oct 10) 278 (41)
 40317-23.
 Journal code: 2985121R. ISSN: 0021-9258.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 OTHER SOURCE: PDB-1IEO
 ENTRY MONTH: 200312
 ENTRY DATE: Entered STN: 20031017
 Last Updated on STN: 20031219
 Entered Medline: 20031202

AB chi-Conopeptide MrIA (***chi*** - ***MrIA***) is a 13-residue peptide contained in the venom of the predatory marine snail Conus marmoreus that has been found to inhibit the norepinephrine transporter (NET). We investigated whether ***chi*** - ***MrIA*** targeted the other members of the monoamine transporter family and found no effect of the peptide (100 microm) on the activity of the dopamine transporter and the serotonin transporter, indicating a high specificity of action. The binding of the NET inhibitors, [3H]nisoxetine and [3H]mazindol, to the expressed rat and human NET was inhibited by ***chi*** - ***MrIA*** with the conopeptide displaying a slight preference toward the rat isoform. For both radioligands, saturation binding studies showed that the inhibition by ***chi*** - ***MrIA*** was competitive in nature. It has previously been demonstrated that ***chi*** - ***MrIA*** does not compete with norepinephrine, unlike classically described NET inhibitors such as nisoxetine and mazindol that do. This pattern of behavior implies that the binding site for ***chi*** - ***MrIA*** on the NET overlaps the antidepressant binding site and is wholly distinct from the substrate binding site. The inhibitory effect of ***chi*** - ***MrIA*** was found to be dependent on Na⁺ with the conopeptide becoming a less effective blocker of [3H]norepinephrine by the NET under the conditions of reduced extracellular Na⁺. In this respect, ***chi*** - ***MrIA*** is similar to the antidepressant inhibitors of the NET. The structure-activity relationship of ***chi*** - ***MrIA*** was investigated by alanine scanning. Four residues in the first cysteine-bracketed loop of ***chi*** - ***MrIA*** and a His in loop 2 played a dominant role in the interaction between ***chi*** - ***MrIA*** and the NET. H alpha chemical shift comparisons indicated that side-chain interactions at these key positions were structurally perturbed by the replacement of Gly-6. From these data, we present a model of the structure of ***chi*** - ***MrIA*** that shows the relative orientation of the key binding residues. This model provides a new molecular caliper for probing the structure of the NET.

L7 ANSWER 2 OF 2 MEDLINE on STN
 ACCESSION NUMBER: 2001486070 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11528421
 TITLE: Two new classes of conopeptides inhibit the
 alfa1-adrenoceptor and noradrenaline transporter.
 AUTHOR: Sharpe I A; Gehrmann J; Loughnan M L; Thomas L; Adams D A;
 Atkins A; Palant E; Craik D J; Adams D J; Alewood P F;
 Lewis R J
 CORPORATE SOURCE: Institute for Molecular Bioscience, University of
 Queensland, Brisbane 4072, Australia.
 SOURCE: Nature neuroscience, (2001 Sep) 4 (9) 902-7.
 Journal code: 9809671. ISSN: 1097-6256.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 OTHER SOURCE: PDB-1IEN; PDB-1IEO
 ENTRY MONTH: 200109
 ENTRY DATE: Entered STN: 20010903
 Last Updated on STN: 20010924
 Entered Medline: 20010920

AB Cone snails use venom containing a cocktail of peptides ('conopeptides') to capture their prey. Many of these peptides also target mammalian receptors, often with exquisite selectivity. Here we report the discovery of two new classes of conopeptides. One class targets alfa1-adrenoceptors (rho-TIA from the fish-hunting Conus tulipa), and the second class targets the neuronal noradrenaline transporter (***chi*** - ***MrIA*** and ***chi*** - ***MrIB*** from the mollusk-hunting C. marmoreus). rho-TIA and ***chi*** - ***MrIA*** selectively modulate these important membrane-bound proteins. Both peptides act as reversible non-competitive inhibitors and provide alternative avenues for

the identification of inhibitor drugs.

=> d his

(FILE 'HOME' ENTERED AT 09:50:17 ON 04 MAY 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 09:50:40 ON 04 MAY 2004

```
L1      4 S CHI-CONOTOXIN
L2      4 DUPLICATE REMOVE L1 (0 DUPLICATES REMOVED)
L3     43 S NEURONAL (W) (AMINE OR NORADRENALINE) (W) TRANSPORTER
L4      1 S L2 (P) L3
L5      9 S CHI-MRIA OR CHI-MRIB
L6      2 DUPLICATE REMOVE L5 (7 DUPLICATES REMOVED)
L7      2 S L6 NOT L2
```

=> s 17 or 12

L8 6 L7 OR L2

=> s 18 (p) pain

```
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L57 (P) PAIN'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L59 (P) PAIN'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L61 (P) PAIN'
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PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L65 (P) PAIN'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L67 (P) PAIN'
L9      3 L8 (P) PAIN
```

=> s 19 not (12 or 17)

L10 0 L9 NOT (L2 OR L7)

=> s lewis r?/au

L11 18025 LEWIS R?/AU

=> s alewood p?/au

L12 627 ALEWOOD P?/AU

=> s sharpe i?/au

L13 90 SHARPE I?/AU

=> s 111 or 112 or 113

L14 18596 L11 OR L12 OR L13

=> s 114 and 11

L15 2 L14 AND L1

=> d his

(FILE 'HOME' ENTERED AT 09:50:17 ON 04 MAY 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 09:50:40 ON 04 MAY 2004

```
L1      4 S CHI-CONOTOXIN
L2      4 DUPLICATE REMOVE L1 (0 DUPLICATES REMOVED)
L3     43 S NEURONAL (W) (AMINE OR NORADRENALINE) (W) TRANSPORTER
L4      1 S L2 (P) L3
L5      9 S CHI-MRIA OR CHI-MRIB
L6      2 DUPLICATE REMOVE L5 (7 DUPLICATES REMOVED)
L7      2 S L6 NOT L2
L8      6 S L7 OR L2
L9      3 S L8 (P) PAIN
L10     0 S L9 NOT (L2 OR L7)
L11    18025 S LEWIS R?/AU
L12     627 S ALEWOOD P?/AU
L13     90 S SHARPE I?/AU
L14    18596 S L11 OR L12 OR L13
L15     2 S L14 AND L1
```

=> log y

COST IN U.S. DOLLARS

SINCE FILE

TOTAL